The role of environment and epigenetics in hypertension

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Cardiovascular disease (CVD) is the major cause of mortality and morbidity globally and affects over 50% of men and 40% of women in their lifetimes. Although age-adjusted mortality for CVD is decreasing in developed countries, there is a sharp rise in developing countries [12]. Approximately three-quarters of global mortality and perhaps approximately 80% of the disease burden (measured as DALYs lost) is expected to occur in low- and middle-income countries (L+ MIC) by the year 2020 [3].

High blood pressure (BP) is the leading cause of CVD and deaths globally. It is associated with 7.5 million deaths (which represents one-eighth of all deaths) per year worldwide [1–4]. The importance of BP as a modifiable risk factor for CVD is well recognized and many effective and inexpensive BP-lowering treatments are commonly available. Therefore, BP control and prevention of related morbidity and mortality is clearly achievable. However, the awareness, treatment and control of hypertension are low in all countries [5]. The reasons for a persisting huge gap in awareness and treatment of hypertension, despite the identification and control of BP being prioritized by many national and global organizations and despite the availability of cheap and effective medications are unclear. The increasing incidence of hypertension and CVD in MIC and LIC seems to be associated with environmental influences and ethnic characteristics [6]. It has been demonstrated in various animal models and from data in human twin and family studies that BP is regulated by different genes [7].

Nonetheless, many environmental risk factors associated with industrialization and urbanization, such as obesity, high dietary salt intake, excessive alcohol consumption, social stress and the aging population, are recognized as important contributory factors to the increases in BP [8]. In low- to middle-income countries, changes such as increased access to westernized diets and the discontinuation of traditional dietary habits may have facilitated the expression of these pathologies and underlie the dramatic increases in the prevalence of hypertension observed in recent years [8–10]. This raises the possibility that genetic predisposition associated with particular ethnic groups might interact with environmental factors to explain the critical increase of hypertension in these countries. There has been considerable interest in the special influence of in utero and early-life environmental exposure. This is represented in the Developmental Origins of Disease hypothesis that emphasizes the critical periods in early life during which body structure and function can be set for life [11]. The early effects of environment have been conceived in terms of epigenetics; the variation of gene expression in response to changes in

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environmental conditions. This term includes any process that alters gene activity without changing the DNA sequences and leads to rapid but reversible modifications of DNA (e.g., methylation) or chromatin that can be transmitted to daughter cells. DNA methylation of a regulatory region for a specific gene can inhibit gene expression. Chromatin is the nuclear complex consisting of DNA wrapped around histone proteins that can be modified by acetylation to influence gene expression [12]. The mechanisms that control epigenetic processes are not yet completely understood, but it is clear that heritable DNA variation might alter the sensitivity to certain environmental triggers or change the nature of the epigenetic responses to a given exposure.

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It is well known that in Latin America, maternal and childhood malnutrition has been an important problem that has not yet been resolved in an important percentage of the poor populations [9,11], and a high prevalence of arterial hypertension has been found in children, adolescents and adults with nutritional stunting [13,14]. This phenomenon, known as fetal programming can be modeled in a range of experimental animal models. Administration of a low protein diet to pregnant rats until term or weaning produces offspring of reduced birth weight in which elevated systolic and diastolic BPs can be identified as early as 4 weeks of age [15]. Hypertension can be prevented in this model by administration of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, but not by nife-dipine. This is highly suggestive of a role of the renin–angiotensin system in disease pathogenesis. Using this model, Bogdarina et al. demonstrated that the expression of the angiotensin receptor 1b (AT1b) gene in the adrenal gland is upregulated by the first week of life resulting in increased receptor protein expression consistent with the increased adrenal angiotensin II (Ang II) responsiveness observed previously [16]. Furthermore, it was shown that the proximal promoter of the AT1b gene in the adrenal was significantly undermethylated, and that in vitro, AT1b gene expression is highly dependent on promoter methylation. These data suggest a link between fetal insults to epigenetic modification of genes and the resultant alteration of gene expression in adult life leading ultimately to the development of hypertension. It seems highly probable that similar influences may be involved in the development of human hypertension.

In this way, Franco et al. reported changes in the sympathoadrenal and RAS in children small for their gestational age [17]. They investigated the plasma levels of angiotensin-converting enzyme (ACE), Ang II and catecholamines in 8- to 13-year-old children to determine correlations between the plasma levels and both birth weight and BP. Circulating noradrenaline levels were significantly elevated in small gestational age girls compared with girls born with a weight appropriate for their gestational age. In addition, Ang II and ACE activity were higher in small gestational age boys. There was a significant association between the circulating levels of both Ang II and ACE activity and systolic BP. Some years ago, we demonstrated [18] that ultrasensitive C-reactive protein (uCRP), a marker of low-grade inflammation, was increased in individuals with hypertension. Based on these findings, we hypothesized that low-degree inflammation could be an independent risk factor for essential hypertension. Visceral fat is a relevant source of proinflammatory cytokines, which are significantly elevated in the serum of subjects with abdominal obesity. The vascular systemic inflammation produced by adipose tissue contributes to the development of hypertension, since inflammation produces endothelial dysfunction. Ang II is produced in adipocytes and the plasma levels of angiotensinogen and Ang II are increased with an increase in body mass index [19]. The production of Ang II in visceral adipocytes appears to be harmful since it is conducive to insulin resistance, water retention and low-degree inflammation – factors associated with hypertension and increased risk of CVD. Recently, we demonstrated in an ex vivo model [20], using segments of internal mammary arteries obtained from individuals with severe coronary artery disease who underwent coronary artery bypass grafts, that the presence of abdominal obesity was related with a higher contractile response to Ang II. Moreover, in the plasma of these patients, progressive decreased levels of adiponectin and increased levels of leptin were observed, associated with an increase in waist circumference. The treatment with the AT1 receptor antagonist, irbesartan, reduced body weight gain, insulin resistance, dyslipidemia and ameliorated adipokine imbalance in obese rats fed a high-fat diet (HFD). The effect on body weight gain in rats was unrelated to a reduction of food intake and seemed to be due to a decrease in adipose tissue weight, as demonstrated by the reductions of epididymal and lumbar adipose tissue mass. In humans, Ang II produced by mature adipocytes appears to inhibit the differentiation of adipocyte precursors, thus decreasing the percentage of small insulin-sensitive adipocytes and promoting the presence of large adipocytes, which decrease insulin sensitivity and produce ectopic deposition of lipids promoting the development of insulin resistance and Type 2 diabetes [6].

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In summary, interactions between Ang II and leptin/adiponectin imbalance seem to play a key role in the metabolic
alterations present in abdominal obesity and in the increased risk of developing hypertension. The increase in the incidence of hypertension in low- and middle-income countries may be associated with rapidly changing environmental conditions and could be the result of the discrepancy between the nutritional environmental during fetal and early life and the adult environment. This discrepancy causes a mismatch between the fetal programming of the subject and the adult circumstances created by the imposition of new life styles. The conflict between the earlier programming and the later presence of abdominal obesity may have produced a higher sensitivity of this population to develop a state of low-degree inflammation, insulin resistance and, consequently, an epidemic of hypertension, diabetes and CVD. The relative roles played by genetic and environmental factors and the interaction between the two are still subjects of great debate and merit further research.

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